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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/621,760	07/17/2003	David L. Lewis	Mirus.030.09.2	9319

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EXAMINER	
POPA, ILEANA	
ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/621,760	LEWIS ET AL.	
	Examiner	Art Unit	
	Ileana Popa	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 5-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 5-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/05/2007 has been entered.

2. Claim 4 has been cancelled. Claim 5 has been amended.

Claims 1-3 and 5-9 are pending and under examination.

Priority

3. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. [1] as follows:

The later-filed application must be an application for a patent for an invention that is also disclosed in the prior application (the parent or original non-provisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the

requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosures of the prior-filed applications, Application No. 10/345,021, 10/186,757, and 10/157,654 (now Patent No. 7,101,995), fail to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The instant claims disclose a composition for delivering a siRNA to a cell and a method of delivering the siRNA to a cell by using the composition, wherein the composition comprises an amphipathic compound, polyvinylamine, and a siRNA. The instant claims are specifically directed to polyvinylamine. However, the applications above do not provide support for the use of a composition comprising polyvinylamine and therefore, the priority date for the instant application is its filing date, i.e., 07/17/2003.

Double Patenting

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees.

A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 1-3 and 5-9 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 6, and 7 of U.S. Patent No. 5,744,335, in view of both Wolfert et al. (Bioconjugate Chem, 1999, 10: 993-100, of record) and Leake et al. (PGPUB 2004/0224405). Although the conflicting claims are not identical, they are not patentably distinct from each other because they are obvious variants.

The instant claims are drawn to (i) a deliverable composition comprising an amphipathic compound, polyvinylamine and siRNA (claim 1); the amphipathic compound is a 1,4 disubstituted piperazine, wherein the substituting groups are C6 to C24 alkenes and R1 and R2 are the same (claims 2 and 3), and (ii) a process for delivering a siRNA to an animal cell by using the above-mentioned composition, and wherein the animal cell is *in vivo*, *in vitro*, *ex vivo* or the cell is a mammalian cell (claims 5-9). The specification discloses that the amphipathic compound may be mixed with the polyvinylamine after the addition of siRNA (i.e., siRNA encapsulation by the amphipathic compound is not required for transfection) (p. 3, paragraph 0020).

The patent claims recite a process for transfecting a polynucleotide into a mammalian cell by delivering a composition comprising and amphipathic compound, a histone as a polynucleotide-binding protein, and the polynucleotide, wherein encapsulation of the polynucleotide by the amphipathic compound is not required for transfection (claims 1 and 2), wherein the amphipathic compound is a 1,4 disubstituted piperazine and wherein the substituting groups are C6 to C24 alkenes (claims 6 and 7). The specification defines that R1 and R2 could be the same and the polynucleotide can be an antisense oligonucleotide (Summary of the invention, lines 54-67, column 7, lines 14-17). The patent claims do not recite polyvinylamine. Wolfert et al. teach that cationic polymers such as polyvinylamine efficiently condensate the nucleic acids and form small complexes with good extracellular stability (Abstract, p. 999, column 1, Results). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of the '335 patent by replacing the histones with polyvinylamine and use it to deliver siRNAs to the nucleus, as taught by Wolfert et al., with a reasonable expectation of success. One of skill in the art would have been motivated to replace the antisense oligonucleotide with a siRNA because siRNA are more efficient than antisense oligonucleotides in inhibiting gene expression. The motivation to use polyvinyl amine in combination with siRNAs is provided by Wolfert et al. who teach that the use of polyvinylamine results in small complexes that are stable in circulation, can undergo extravasation in the target tissues and can easily enter into the nucleus of target cells (Abstract, p. 1002, column 2, p. 1003, column 2) and by Leake et al., who teach the necessity of targeting the siRNAs to the nucleus to target non-coding

nucleic acid sequences, such as promoters or enhancers (p. 1, paragraphs 0005, 0006, and 0012-0015, p. 2, paragraphs 0023-0029, p. 4, paragraph 0061, p. 4, paragraph 0062). With respect to the limitations recited in the instant claims 6-8, they are not innovative over the prior art; one of skill in the art would have known that such compositions could be used to deliver siRNAs *ex vivo*, *in vivo*, or *in vitro*. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant argues that Wolfert et al. do not teach that DNA/PVA complexes are suitable for intranuclear delivery, but rather that they are suitable for intranuclear transcription. In fact, Applicant argues, Wolfert et al. teach that PVA is the least effective at transfecting the cells. Therefore, Applicant submits that the teachings of Wolfert et al. contradict the Examiner's statement that there is no disclosure of PVA being unsuitable for polynucleotide delivery. With respect to the teachings of the '335 patent Applicant argues that 1,4 disubstituted piperazine does not generally enhance polycation transfection efficiency and that PVA will not substitute for histone in the complex taught by the '335 patent to form a complex with the same transfection properties. In support for this assertion Applicant submits a 132 Declaration showing that the composition of the '335 patent is not an effective siRNA delivery agent, despite the teachings in the specification that the composition is useful for the delivery of oligonucleotides and RNA. Therefore, Applicant submits that the 132 Declaration demonstrate that the instant invention is not obvious over the '335 patent in view of Wolfert et al. and requests the withdrawal of the rejection.

Applicant's arguments are acknowledged, however, they are not found persuasive for the following reasons:

Wolfert et al. teach that small DNA/carrier complexes (such as DNA/PVA complexes) are stable and capable of entering the nucleus due to their small size, and therefore, such complexes mediate efficient transcription; therefore, Wolfert et al. do teach that DNA/PVA complexes are suitable for intranuclear delivery (see p. 1002, column 2, p. 1003, column 2). The '335 patent teaches delivery to the nucleus by derivatizing the histones with nuclear localization signals (column 2, lines 25-35). It is also noted that the prior art teaches the use of PVA to deliver nucleic acids to cells (see for example, Calatrava, PGPUB 2003/0219410, p. 8, paragraph 0072, p. 9, paragraph 0074). Based on these teachings, one of skill in the art would know that PVA is suitable for nucleic acid delivery; one of skill in the art would also know to target the PVA-based complexes to the nucleus by linking PVA to nuclear localization signals. For these reasons, Applicant's argument that the teachings of Wolfert et al. indicate that PVA is unsuitable for nucleic acid delivery is not found persuasive. With respect to the teachings of the '335 patent, the patent teaches that it is the combination DNA-binding proteins and 1,4 disubstituted piperazine that enhance the delivery of DNA to cells, wherein histone cannot mediate efficient transfection when used without amphipathic compounds (column 2, lines 5-18, column 27, lines 35-55, column 28, lines 9-12). For this reason, Applicant's argument that it is the histone that enhances the transfection efficiency and that PVA will not substitute for histone in the complex taught

by the '335 patent to form a complex with the same transfection properties is not found persuasive.

The 132 is insufficient to overcome the instant rejection because the data presented do not pertain to the instant invention. The data presented in the Declaration describe the results obtained with a complex between an amphipathic compound, siRNA, and either histone or PEI. The Declaration states that the histone + amphipathic compound is the same as that used in the '335 patent, while the combination of ePEI + amphipathic compound is the same as the one described in the application 10/621,760; however, since both the '335 patent and the '760 application describe more than one amphipathic compounds, it is not clear what amphipathic compound is used in the experiment. The instant invention is not drawn to complexes comprising histones or ePEI; the instant invention is drawn to a complex between 1,4 disubstituted piperazine and PVA. Therefore, although the132 Declaration demonstrates that the combination of histones and amphipathic compounds are not able to deliver siRNAs to cells, the data presented in the Declaration do not demonstrate that PVA in combination with 1,4 disubstituted piperazine would not be able to deliver siRNA or DNA to cells. The instant rejection is based on a combination of references which teaches PVA, 1,4 disubstituted piperazine, and siRNA, which is the same as the claimed composition and it is not clear why the two compositions would not have the same properties. For these reasons the rejection is maintained.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1-3 and 5-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wolf et al. (US Patent 5,744,335, of record) in view of each Wolfert et al. (Bioconjugate Chem, 1999, 10: 993-1004, of record), Pollard et al. (J Biol Chem, 1998, 27: 7507-751, of record), and Leake et al. (PGPUB 2004/0224405, of record).

Wolf et al. teach a method for delivering a polynucleotide into a cell (i.e., the cell can be *in vivo*, *in vitro*, *ex vivo* or the cell is a mammalian cell), by delivering to the cell a composition comprising an amphipathic compound, a histone, and a selected polynucleic acid, wherein the polynucleic acid can be RNA in the form of oligonucleotide (i.e., the RNA can be siRNA); the amphipathic compound is a 1,4 disubstituted piperazine, wherein the substituting groups are C6 to C24 alkenes (claims 1-3 and 5-9) (Summary of the invention, column 2, lines 40-52, column 7, lines 17-20). Wolf et al. do not teach polyvinylamine (PVA). Wolfert et al. teach that cationic polymers such as PVA efficiently condensate the nucleic acids and form small complexes with good extracellular stability suitable for DNA delivery to the nucleus (Abstract, p. 999, column 1, Results, p. 1003, column 2). In addition to the teachings of Wolfert et al., Pollard et al. teach that it is the compaction of DNA (i.e., the particle size) that improves nuclear

targeting (p. 7511, column 1). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Wolf et al. by substituting histones with PVA to obtain small and stable complexes, for nuclear targeting. One of skill in the art would have been motivated to do so because the prior art teaches the desirability to target siRNA to the cell nucleus. For example Wolff et al. teach nuclear targeting mediated by a nuclear localization signal linked to the histone (column 2, lines 15-27) and Leake et al. teach nuclear targeting to inhibit non-coding nucleic acid sequences, such as promoters or enhancers (p. 1, paragraphs 0005, 0006, and 0012-0015, p. 2, paragraphs 0023-0029, p. 4, paragraph 0061, p. 4, paragraph 0062). One of skill in the art would have been expected to have a reasonable expectation of success because the art teaches that ternary complexes between nucleic acids, amphipathic molecules and polycations can be successfully obtained and used to transfer the desired nucleic acid into cells. With respect to the limitation of the composition facilitating entry of the siRNA into the cell (claim 5), since the composition taught by the combined teachings above is identical to the claimed composition, it must necessarily deliver the siRNA to the cell. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant traversed the instant rejection on the same grounds as above. The rejection is maintained for the same reasons as above.

Conclusion

8. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure: Calatrava, PGPUB 2003/0219410. The art was cited in response to Applicant's arguments that there is no suggestion in the art to motivate one of skill in the art to use PVA as a transfection reagent based on the teachings of Wolfert et al.

9. No claim is allowed. No claim is free of prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ileana Popa whose telephone number is 571-272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ileana Popa, PhD

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AU1633